## 32892.00024

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant

: Eugenio A. Cefali\*

Application No.

: 08/962,421 Confirmation No. :

Filed

:October 31, 1997

For

: INTERMEDIATE RELEASE NICOTINIC ACID

COMPOSITIONS FOR TREATING HYPERLIPIDEMIA WHICH

EXHIBIT AN IN VIVO STAIR-STEPPED ABSORPTION

CURVE

Group

: 1615

Examiner

: James M. Spear

Hon. Commissioner for Patents P.O. Box 2327 Arlington, Virginia 22202

> INFORMATION DISCLOSURE STATEMENT <u>UNDER 37 C.F.R. §§ 1.56</u> AND 1.97(b)

Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), applicant, through his representatives, makes of record the following documents, copies of which are included:

The inventor on file for this application is Eugenio A. Cefali. A Petition to Correct Inventorship under 37 C.F.R. § 1.48(a) to add David J. Bova as a co-inventor was filed on January 16, 2003 and is currently pending.

For the convenience of the Examiner, a completed Form PTO-1449 listing these documents is attached hereto in duplicate

## United States Patents

		/ /
Fields et al.	Re. 29,652	05/30/1978
Scherm et al.	Re. 32,581	01/19/1998
Woodward et al.	2,510,164	06/06/1950
Clymer et al.	2,540,979	02/06/1951
Buckwalter	2,749,274	06/05/1956
	2,798,837	07/09/1957
Sahyun	· · · · · · · · · · · · · · · · · · ·	07/09/1957
Robinson	2,798,838	09/10/1957
Robinson et al.	2,805,977	09/10/1957
Kennon et al.	2,851,453	•
Cooper et al.	2,857,313	10/21/1958
Klioze et al.	2,887,436	05/19/1959
Schuyler	2,957,804	10/25/1960
Costello	3,062,720	11/06/1962
Christenson et al.	3,065,143	11/20/1962
Harbit	3,108,046	10/22/1963
Siegel et al.	3,116,204	12/31/1963
Sheth et al.	3,134,719	05/26/1964
Debay et al.	3,143,469	08/04/1964
<del>-</del>	3,147,187	09/01/1964
Playfair 	3,147,167	07/06/1965
Eisen	· · · · · · · · · · · · · · · · · · ·	10/05/1965
Blank et al.	3,210,413	
Nakano et al.	3,272,832	09/13/1966
Krause et al.	3,336,200	08/15/1967
Nürnberg	3,424,842	01/28/1969
Fossel	3,495,011	02/10/1970
Christenson et al.	3,590,117	06/29/1971
Kariya et al.	3,626,071	12/07/1971
Nakamota et al.	3,629,393	12/21/1971
Waring	3,629,453	12/21/1971
Poole	3,634,584	01/11/1972
Barnhart	3,639,636	02/01/1972
	3,709,991	01/09/1973
Miller	3,705,551	03/20/1973
Thiffault	·	11/20/1973
Nakamoto et al.	3,773,920	•
Douglas et al.	3,795,691	03/05/1974
Mikite et al.	3,806,601	04/23/1974
Winitz	3,849,554	11/19/1974
Weigand	3,859,437	01/07/1975
Barnhart et al.	3,862,332	01/21/1975
Albright et al.	3,868,416	02/25/1975
Lowey et al.	3,870,790	03/11/1975
Fields et al.	3,923,972	12/02/1975
Albright et al.	3,924,001	12/02/1975
Kummer et al.	3,930,017	12/30/1975
Davidson	3,951,821	04/20/1976
	3,957,976	05/18/1976
Sugimoto	3, 33, , 3, 10	05/ 25/ 25/ 0

Coulston et al.	3,959,492	05/25/1976
Bloch et al.	3,965,255	06/22/1976
Theeuwes	3,977,404	08/31/1976
Broughton et al.	3,987,160	10/19/1976
Kleemann et al.	3,992,536	11/16/1976
Möller et al.	4,002,641	01/11/1977
Theeuwes et al.	4,008,719	02/22/1977
Galantay et al.	4,011,339	03/08/1977
Theeuwes et al.	4,014,334	03/29/1977
Heller et al.	4,014,987	03/29/1977
Voorhees	4,034,087	07/05/1977
Theeuwes	4,034,758	07/12/1977
Theeuwes Theeuwes et al.	4,058,122	11/15/1977
Ferutti et al.	4,067,876	01/10/1978
Theeuwes et al.	4,077,407	03/07/1978
Kondo et al.	4,102,806	07/25/1978
Fields et al.	4,115,550	09/19/1978
Theeuwes et al.	4,116,241	09/26/1978
Fields et al.	4,117,111	09/26/1978
Sheth et al.	4,126,672	11/21/1978
Sheth et al.	4,140,755	02/20/1979
Ayer et al.	4,160,020	07/03/1979
Theeuwes	4,160,452	07/10/1979
Ferruti	4,166,902	09/04/1979
Sheth et al.	4,167,558	09/11/1979
Scallen et al.	4,169,944	10/02/1979
Diamond et al.	4,178,387	12/11/1979
Heller et al.	4,180,064	12/25/1979
Thiele et al.	4,182,902	01/08/1980
Theeuwes	4,203,439	05/20/1980
Shepherd	4,205,085	05/27/1980
Shepherd	4,211,783	07/08/1980
Schor	4,226,849	10/07/1980
Shepherd	4,230,878	10/28/1980
Howard	4,237,118	12/02/1980
DeNeale et al.	4,248,857	02/03/1981
Robbins et al.	4,251,519	02/17/1981
Cavazza	4,255,449	03/10/1981
Theeuwes	4,256,108	03/17/1981
Lowey	4,259,314	03/31/1981
Ogawa et al.	4,261,970	04/14/1981
Cavazza	4,268,524	05/19/1981
Gatzen et al.	4,272,548	06/09/1981
Engel et al.	4,279,898	07/21/1981
Vilani	4,282,233	08/04/1981
Frank et al.	4,283,382	08/11/1981
Hoefle	4,285,951	08/25/1981
Mulinos	4,291,030	09/22/1981

Shepherd	4,305,959	12/15/1981
Dunn et al.	4,308,251	12/29/1981
DeNeale et al.	4,309,404	01/05/1982
Shepherd	4,310,545	01/12/1982
Shepherd	4,318,914	03/09/1982
Swanson et al.	4,326,525	04/27/1982
Shepherd	4,348,399	09/07/1982
Hess et al.	4,353,887	10/12/1982
Schor	4,357,469	11/02/1982
Stricker et al.	4,361,546	11/30/1982
Cerami	4,362,711	12/07/1982
Gruber et al.	4,367,217	01/04/1983
<sup>†</sup> Schor et al.	4,369,172	01/18/1983
Dunn	4,375,468	03/01/1983
Shepherd	4,382,143	05/03/1983
†Schor et al.	4,389,393	06/21/1983
Hata et al.	4,428,951	01/31/1984
Zeitoun et al.	4,432,966	02/21/1984
Shepherd	4,440,940	04/03/1984
Kent	4,452,775	06/05/1984
Iida et al.	4,454,108	06/12/1984
McFarlane et al.	4,455,298	06/19/1984
Porter	4,457,907	07/03/1984
Dunn	4,461,759	07/24/1984
David et al.	4,465,660	08/14/1984
Hooper	4,472,436	09/18/1984
Hercelin et al.	4,478,819	10/23/1984
Shepherd	4,485,105	11/27/1984
†** Jain et al.	4,505,890	03/19/1985
Dunn	4,522,804	06/11/1985
Dunn et al.	4,525,345	06/25/1985
Powell et al.	4,539,198	09/03/1985
Davis et al.	4,540,566	09/10/1985
Zierenberg et al.	4,547,359	10/15/1985
Hsiao et al.	4,556,678	12/03/1985
Herschler	4,568,547	02/04/1986

This symbol indicates documents cited by Barr Laboratories in connection with litigation between Kos Pharmaceuticals and Barr Laboratories currently pending in the Southern District of New York. Kos Pharmaceuticals is the assignee of record of the pending application.

<sup>\*\*</sup> This symbol indicates documents cited to the Examiner for the first time.

	000	02/18/1986
Hsiao	4,571,333	03/18/1986
Guittard et al.	4,576,604	07/29/1986
Burger et al.	4,603,142	08/12/1986
Schmidt et al.	4,605,666	09/09/1986
<sup>†</sup> Jain et al.	4,610,870	
Sasaki et al.	4,624,950	11/25/1986
Hanna et al.	4,657,757	04/14/1987 06/16/1987
Guittard et al.	4,673,405	06/16/1987
Alderman et al.	4,678,516	• •
Lowey	4,680,323	07/14/1987 08/04/1987
Bhutani	4,684,516	08/04/1987
Powell et al.	4,690,824	09/01/1987
Ukigaya et al.	4,692,337	09/08/1987
Uemura et al.	4,695,467	09/22/1987
Hanna et al.	4,695,591	09/22/1987
Maruyama et al.	4,695,910	09/22/1987
Sander et al.	4,696,762	11/03/1987
Alderman	4,704,285	11/24/1987
Cohen et al.	4,708,834	12/01/1987
Finnan et al.	4,710,519 4,713,245	12/15/1987
Ando et al.	4,713,245	03/08/1988
Makino et al.	4,729,893	03/29/1988
Alderman	4,744,907	05/17/1988
Klimchak et al.	4,747,881	05/31/1988
Shaw et al.	4,747,881	06/07/1988
Rotman	4,752,479	06/21/1988
Briggs et al.	4,753,801	06/28/1988
Oren et al.	4,755,544	07/05/1988
Makino et al.	4,756,911	07/12/1988
†Drost et al.	4,758,581	07/19/1988
Scherm et al.	4,759,923	07/26/1988
Buntin et al.	4,764,374	08/16/1988
Grimberg	4,775,483	10/04/1988
Mookerjea et al.	4,775,535	10/04/1988
Lowey Toda et al.	4,777,042	10/11/1988
Ventouras	4,784,858	11/15/1988
Khan et al.	4,789,549	12/06/1988
Howard et al.	4,792,452	12/20/1988
Elben et al.	4,792,554	12/20/1988
Takahasi et al.	4,794,115	12/27/1988
Gaylord et al.	4,795,327	01/03/1989
Cohen et al.	4,795,642	01/03/1989
Zentner	4,795,644	01/03/1989
Hsiao et al.	4,803,079	02/07/1989
Falk et al.	4,803,081	02/07/1989
Rossi et al.	4,812,316	03/14/1989
Zentner	4,814,183	03/21/1989

Ghebre-Sellassie et a	1. 4,814,354	03/21/1989
Day et al.	4,824,672	04/25/1989
Shah et al.	4,824,677	04/25/1989
Elger et al.	4,828,836	05/09/1989
Finnan	4,830,859	05/16/1989
Martani et al.	4,834,965	05/30/1989
Elger et al.	4,834,985	05/30/1989
Ortega	4,837,032	06/06/1989
Colombo et al.	4,839,177	06/13/1989
Nishimura et al.	4,842,863	06/27/1989
Elger et al.	4,844,907	07/04/1989
Gaylord et al.	4,849,229	07/18/1989
Urquhart et al.	4,851,232	07/25/1989
Khan et al.	4,851,233	07/25/1989
Lowey	4,855,143	08/08/1989 08/15/1989
Khanna et al.	4,857,336	08/15/1989
Izydore et al.	4,866,058	10/03/1989
Edgren et al.	4,871,548	11/21/1989
Jang	4,882,167	12/12/1989
Ventouras	4,886,669	12/12/1989
Rotini et al.	4,888,178	01/09/1990
Ohm et al.	4,892,741	03/27/1990
Kuhrts	4,911,917	04/10/1990
Ayer et al.	4,915,952	04/10/1990
Nestler et al.	4,920,115	04/24/1990
Beyer, Jr.	4,920,123	05/15/1990
Boeckh et al.	4,925,905	06/19/1990
Ahrens	4,935,246 4,940,588	07/10/1990
Sparks et al.	4,940,388	07/17/1990
Ragnarsson et al.	4,942,040	08/07/1990
Partain, III et al.	4,946,870	08/07/1990
Izydore et al.	4,940,903	08/21/1990
Yang et al.	4,952,402	08/28/1990
Sparks et al.	4,959,478	09/25/1990
Möller et al.	4,963,367	10/16/1990
Ecanow	4,965,252	10/23/1990
Kuhrts	4,966,768	10/30/1990
Michelucci et al.	4,968,508	11/06/1990
Oren et al.	4,970,081	11/13/1990
Frisbee	4,973,468	11/27/1990
Chiang et al.	4,973,469	11/27/1990
Mulligan et al.	4,983,398	01/08/1991
Gaylord et al. Cho et al.	4,990,535	02/05/1991
Khanna	4,992,278	02/12/1991
Sablotsky	4,994,267	02/19/1991
Baichwal et al.	4,994,276	02/19/1991
Sinnreich	4,996,058	02/26/1991
STHITETON	, - ,	

Alberts et al.	4,997,658	03/05/1991	•
Berger et al.	4,999,380	03/12/1991	
Agrawala	5,002,774	03/26/1991	
Lui	5,009,895	04/23/1991	
Lee	5,010,105	04/23/1991	
Catt et al.	5,011,947	04/30/1991	
Mulligan et al.	5,015,479	05/14/1991	
Kuhrts	5,023,245	06/11/1991	
Miura et al.	5,025,012	06/18/1991	
Trivedi	5,030,653	07/09/1991	
Dansereau et al.	5,032,406	07/16/1991	
Izydore et al.	5,034,528	07/23/1991	
Meyer	5,039,341	08/13/1991	
Calanchi et al.	5,047,248	09/10/1991	
Lee et al.	5,049,696	09/17/1991	
Kuhrts	5,096,714	03/17/1992	
Cho et al.	5,100,675	03/31/1992	
Beyer, Jr.	5,110,817	05/05/1992	
Sit et al.	5,110,940	05/05/1992	
Broaddus	5,116,610	05/26/1992	
<sup>†</sup> Evenstad et al.	5,126,145	06/30/1992	
Mulligan et al.	5,128,142	07/07/1992	
Pan et al.	5,130,333	07/14/1992	
Sournac et al.	5,132,116	07/21/1992	
Paradissis et al.	5,133,974	07/28/1992	
Gakic et al.	5,145,678	09/08/1992	
Muhammad et al.	5,167,964	12/01/1992	
Dennis et al.	5,169,638	12/08/1992	
Baichwal et al.	5,169,639	12/08/1992	
France et al.	5,169,640	12/08/1992	
Takemori et al.	5,171,570	12/15/1992	
Asami et al.	5,178,854	01/12/1993	
Helms et al.	5,182,298	01/26/1993	
Pearmain	5,188,839	02/23/1993	
Commons et al.	5,190,940	03/02/1993	
Pan et al.	5,190,970	03/02/1993	
Bertolini et al.	5,196,440	03/23/1993	
Akkerboom et al.	5,211,958	05/18/1993	
Bar-Shalom et al.	5,213,808	05/25/1993	
Chiang	5,256,689	10/26/1993	
Berger et al.	5,258,401	11/02/1993	
Dennick	5,260,305	11/09/1993	
Govil et al.	5,262,165	11/16/1993	
Joshua et al.	5,262,435	11/16/1993	
Graille et al.	5,264,226	11/23/1993	
<sup>†</sup> O'Neill et al.	5,268,181	12/07/1993	
Dawson et al.	5,278,067	01/11/1994	
Soyka et al.	5,286,736	02/15/1994	

5,314,697 05/24/1994

Kwan et al.

## FOREIGN PATENT PUBLICATIONS

603,690 0 109 320 0 126 453 0 349 235 A2 0 577 504 A1 1,302,362 40-2053 46-18151 55-049312 2 141 338 2 154 874	Canada EP EP EP France Japan Japan Japan UK UK	08/16/1960 05/23/1984 11/28/1984 01/03/1990 01/05/1994 07/23/1962 02/03/1965 05/20/1971 09/04/1980 12/19/1984 09/18/1985
2 154 874 WO84/00104	UK PCT	09/18/1985 01/19/1984

## OTHER DOCUMENTS

English language translation of Abstract of Japanese Patent No. JP63310827 A 881219 Derwent DW8905 (1988).

English language translation of Abstract of Japanese Patent No. JP5221854 A 930831 Derwent DW9339 A61K9/22 (1993).

Slow Niacin Advertisement, Am. Druggist, 141-142 (1988).

Regulatory Letter to Upsher-Smith Laboratories (Jun. 6, 1988).

 $^{\dagger}$  "Issues in Cholesterol Management: Reappraisal of Niacin," (Ed. Hunninghake), Upsher-Smith Laboratories, 1-7 (1990).

\*\*\* "Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," The Expert Panel, Arch. Intern. Med., 148:36-69 (1988).

Handbook of Nonprescription Drugs, Nutritional Supplements, 9th Edition, American Pharmaceutical Association, 470-471 (1990).

"Clofibrate and Niacin in Coronary Heart Disease," The Coronary Project Research Group, JAMA, 231(4):360-381 (1975).

Abumrad, N.A., et al., "Studies on Serum lipids, Insulin, and Glucagon and on Muscle Triglyceride in Rats Adapted to High-fat and High-carbohydrate Diets," J. Lipid Res., 19:423-432 (1978).

Alderman, J.D., et al., 'Major Favorable Changes in cholesterol and HDL in Coronary Patients Using a Modified Niacin Regimen," Clin. Res., Abstract 1883, III-471 (1985).

†Alderman, J.D., et al., "Effect of a Modified, Well-Tolerated Niacin Regimen on Serum Total Cholesterol, High Density Lipoprotein Cholesterol and the Cholesterol to High Density Lipoprotein Ratio," Am. J. Cardiol., 64(12):725-729 (1989).

Altschul, R., et al., "Influence of Oxygen Inhalation on Cholesterol Metabolism," Letters to the Editors, Arch. Biochem. Biophys., 51:308-309 (1954).

Altschul, R., et al., "Influence of Nicotinic Acid on Serum Cholesterol in Man," Letters to the Editors, Arch. Biochem. Biophys. 54:558-559 (1955).

Altschul, R., et al., "Niacin In Vascular Disorders And Hyperlipemia," Charles C. Thomas Publ., Springfield, IL., 42-47; 116-133 (1964).

Andreotti, F., et al., "Major Circadian Fluctuations in Fibrinolytic Factors and Possible Relevance to Time of Onset of Myocardial Infarction, Sudden Cardiac Death and Stroke," Am. J. Cardiol., 62:635-637 (1988).

Angleton, P., et al., "Diurnal Variation of Tissue-Type Plasminogen Activator and Its Rapid Inhibitor (PAI-1)," Circulation, 79(1):101-106 (1989).

Barter, P.J., et al., "Diurnal Fluctuations in Triglyceride, Free Fatty Acids, and Insulin During Sucrose Consumption and Insulin Infusion in Man," J. Clin. Invest., 50:583-591 (1971).

Berge, K.G., et al., "Hypercholesteremia and Nicotinic Acid: A Long-Term Study," Am. J. Med., 31:24-35 (1961).

Blankenhorn, D.H., et al., "Beneficial Effects of Combined Colestipol-Niacin Therapy on Coronary Atherosclerosis and Coronary Venous Bypass Grafts," JAMA, 257(23):3233-3240 (1987).

Blum, C.B., et al., "Current Therapy for Hypercholesterolemia," JAMA, 261(24):3582-3587 (1989).

Brown, G., et al., "Regression of Coronary Artery Disease as a Result of Intensive Lipid-Lowering Therapy in Men with High Levels of Apoliprotein B," N. Engl. J. Med., 323(19):1289-1298 (1990).

Buri, P., et al., "Formulation des comprimés à libération prolongée II. Matrices hydrophiles," ("Formulation of sustained-release tablets. II. Hydrophilic matrices") Pharm. ACTA Helv., 33(7-8):189-197 (1980) (with English translation of the abstract).

Canner, P.L., et al., "Fifteen Year Mortality in Coronary Drug Project Patients: Long-Term Benefit With Niacin," J. Am. Coll. Cardiol., 8(6):1245-1255 (1986).

Carlson, L.A., "Inhibition of the Mobilization of Free Fatty Acid from Adipose Tissue," Ann. N.Y. Acad. Sci., III(471):119-142.

Carlson, L.A., et al., "The Effect of Nicotinic Acid on the Plasma Free Fatty Acids: Demonstration of a Metabolic Type of Symphathicolysis," Acta Med. Scand., 172:641-645 (1962).

Carlson, L.A., "Studies on the Effect of Nicotinic Acid on Catecholamine Stimulated Lipolysis in Adipose Tissue in Vitro," Acta Med. Scand., 173:719-722 (1963).

Carlson, L.A., et al., "Acute Effects of Nicotinic Acid in the Rat. I. Plasma and Liver Lipids and Blood Glucose," Acta Med. Scand., 179:453-461 (1966).

Carlson, L.A., "Determination of Free Nicotinic Acid in Blood Plasma," Clin. Chim. Acta, 13:349-351 (1966).

Carlson, L.A., et al., "Consequences of Inhibition of Normal and Excessive Lipid Mobilization. Studies with Nicotonic Acid," Prog. Biochem. Pharmacol., 3:151-166 (1967).

Carlson, L.A., et al., "Effect of a Single Dose of Nicotinic Acid on Plasma Lipids in Patients with Hyperlipoproteinemia," Acta Med. Scand., 183:457-465 (1968).

Carlson, L.A., et al., "Plasma Lipids and Urinary Excretion of Catecholamines in Man during Experimentally Induced Emotional Stress, and Their Modification by Nicotinic Acid," J. Clin. Invest., 47:1795-1805 (1968).

Carlson, L.A., et al., "Pronounced Lowering of Serum Levels of Lipoprotein Lp(a) in Hyperlipidaemic Subjects Treated with Nicotinic Acid," J. Int. Med., 226(5):271-276 (1989).

Cayen, M.N., "Metabolic Disposition of Antihyperlipidemic Agents in Man and Laboratory Animals," *Drug Metab. Rev.*, 11(2):291-323 (1980).

Cayen, M.N., et al., "Effect of AY-25,712 on Fatty Acid Metabolism in Rats," Atherosclerosis, 45(3):281-290 (1982).

Chandler, W.L., et al., "Insulin, Cortisol and Catecholamines Do Not Regulate Circadian Variations in Fibrinolytic Activity,"

Thrombosis Res., 58(1):1-12 (1990).

Chowhan, Z.T., et al., "Hardness Increase Induced by Partial Moisture Loss in Compressed Tablets and Its Effect on In Vitro Dissolution," J. Pharm. Sci., 67(10):1385-1389 (1978).

Chowhan, Z.T., "Role of Binders in Moisture-Induced Hardness Increase in Compressed Tablets and Its Effect on *In Vitro* Disintegration and Dissolution," *J. Pharm. Sci.*, 69(1):1-3 (1980).

Chowhan, Z.T., et al., "Compression Properties of Granulations Made with Binders Containing Different Moisture Contents," J. Pharm. Sci., 70(10):1134-1139 (1981).

Christensen, N.A., et al., "Nicotinic Acid Treatment of Hypercholesteremia, Comparison of Plain and Sustained-Action

Preparations and Report of Two Cases of Jaundice" JAMA, 177(8):76-80 (1961).

Cooper, K.H., "The Wisdom and Risk of Drug and Vitamin Therapy," Dr. Kenneth H. Cooper's Preventive Medicine Program, Controlling Cholesterol, 244-252, Bantam Books, (1988).

Criscuoli, M., et al., "Glunicate (LG 13979) Protects the Arterial Wall from Cholesterol-Induced Atherosclerotic Changes in the Rabbit Without Affecting Plasma Lipids," Atherosclerosis, 53(1):59-68 (1984).

Dalton, T.A., et al., "Hepatotoxicity Associated with Sustained-Release Niacin," Am. J. Med., 93(1):102-104 (1992).

Davis, S.S., et al., Modern Concepts in Nitrate Delivery Systems, 30-37, (Eds. A.A.J. Goldberg, D.G. Parsons), 1983 Royal Soc. of Med. Int'l. Cong. & Symp. Series No. 54, published jointly by Academic Press Inc. (London) Ltd. and Royal Society of Medicine.

Dow, "Formulating for Controlled Release with METHOCEL Premium Cellulose Ethers," Dow Chemical Company publications, 1-33 (1995).

Dow, "METHOCEL as a Binding Agent for Tablet Production by Wet Granulation," Dow Chemical Company publication, 1-15 (1985).

Dow, "Viscosity: Molecular Weight-Viscosity Relationship," Handbook on METHOCEL\* Cellulose Ether Products, Dow Chemical Company publication (1974).

Dow, "Technical Information: Methods of Formulating Controlled Release Products Outside the Forest Lab Patent US 4,389,393 Claims."

Dow, "Formulating Sustained Release Pharmaceutical Products with METHOCEL," Dow Chemical Company publication.

Dow, product designation changes for METHOCEL cellulose ethers, Dow Chemical Co. publication (1985) (CZ).

Dow, product designation changes for METHOCEL cellulose ethers, Dow Chemical Co. publication (DG) (1960).

Ekström-Jodal, B., et al., "Influence of Nicotinic Acid and Pentaerythritoltetranicotinate (Perycit®, Bofors) on the Cardiac Output in Man," *Pharmacologia Clinica*, 2:86-89 (1970).

Etchason, J.A., et al., "Niacin-Induced Hepatitis: A Potential Side Effect with Low-Dose Time-Release Niacin," Mayo Clin. Proc., 66:23-28 (1991).

Figge, H.L., et al., "Comparison of Excretion of Nicotinuric Acid After Ingestion of Two Controlled Release Nicotinic Acid Preparations in Man," J. Clin. Pharmacol., 28:1135-1140 (1988).

Figge, H.L., et al., "Nicotinic Acid: A Review of Its Clinical Use in the Treatment of Lipid Disorders," Pharmacotherapy, 8(5):287-294 (1988).

Fleischman, A.I., et al., Low Dose Sustained Release Nicotinic Acid As An Effective Hypo Lipidemic Agent In Man," Fed. Proc., 34(1):248 (1975).

†\*\* Gray, D.R., et al. "Efficacy and Safety of Controlled-release Niacin in Dyslipoproteinemic Veterans," Ann. Intern. Med. 121: 252-258 (1994).

Gudsoorkar, V.R., et al., "Influence of Binders on Some Physical Parameters of Lactose and Sulfadimidine Tablets," Indian Drugs & Pharmaceuticals Industry, 3-4 (Jul.-Aug. 1980).

Hamsten, A., et al., "Increased Plasma Levels of a Rapid Inhibitor of Tissue Plasminogen Activator in Young Survivors of Myocardial Infarction," N. Engl. J. Med., 313(25):1557-1563 (1985).

Henkin, Y., et al., "Rechallenge With Crystalline Niacin After Drug-Induced Hepatitis From Sustained-Release Niacin," JAMA, 264(2):241-243 (1990).

Henkin, Y., et al., "Niacin Revisited: Clinical Observations on an Important but Underutilized Drug," Am. J. Med., 91:239-246 (1991).

Hodis, H.N., "Acute Hepatic Failure Associated With the Use of Low-Dose Sustained-Release Niacin," Letter to the Editors, JAMA 264(2):181 (1990).

Huber, H.E., et al., "Utilization of Hydrophilic Gums for the Control of Drug Release from Tablet Formulations I. Disintegration and Dissolution Behavior," J. Pharm. Sci., 55(9):974-976 (1966).

Ibrahim, S.A., et al., "Release Characteristics of Oxyphenbutazone from Different Suppository Bases," *Pharmazie*, 35(8):567 (1980).

Jacobson, T.A., et al., "Combination Therapy with Fluvastatin and Niacin in Hypercholesterolemia: A Preliminary Report on Safety," Am. J. Cardiol., 73:25D-29D (1994).

Kane, J.P., et al., "Normalization of Low-Density-Lipoprotein Levels in Heterozygous Familial Hypercholesterolemia with a Combined Drug Regimen," N. Engl. J. Med., 304(5):251-258 (1981).

Kassem, A.A., et al., "Enhancement of Release Rate of Spironolactone from Its Tablets by the Formation of Solid Dispersions with Water-Soluble Polymers," Jami et Al-Qahira, Faculty of Pharmacy, Cairo University, Bulletin, Cairo, 19(1):275-306 (1980).

Keenan, J.M., et al., "Niacin Revisited: A Randomized, · Controlled Trial of Wax-Matrix Sustained-Release Niacin in Hypercholesterolemia," JAMA Spec. J. Abst., 266(16):2209 (1991).

Keenan, J.M., et al., "Niacin Revisited A Randomized, Controlled Trial of Wax-Matrix Sustained-Release Niacin in Hypercholesterolemia," Arch. Intern. Med., 151:1424-1432 (1991).

Keenan, J.M., et al., "Treatment of Hypercholesterolemia: Comparison of Younger versus Older Patients Using Wax-Matrix Sustained-Release Niacin," J. Am. Geriat. Soc., 40:12-18 (1992).

King, R.E., "Tablets, Capsules, and Pills," Remington's Pharm.
Sci., 1576-1587 (1975).

Kirschstein, W., et al., "Impaired Fibrinolytic Capacity and Tissue Plasminogen Activator Release in Patients with Restenosis after Percutaneous Transluminal Coronary Angioplasty (PTCA)," Thromb. Haemost., 62(2):772-775 (1989).

Knopp, R.H., et al., "Contrasting Effects of Unmodified and Time-Release Forms of Niacin on Lipoproteins in Hyperlipidemic Subjects: Clues to Mechanism of Action of Niacin," Metabolism, 34(7):642-650 (1985).

Korsmeyer, R.W., et al., "Mechanisms of Potassium Chloride Release from Compressed, Hydrophilic, Polymeric Matrices: Effect of Entrapped Air," J. Pharm. Sci., 72(10):1189-1191 (1983).

Kowalski, R.E., The 8-Week Cholesterol Cure, Harper & Row, Publishers, 95-115 (1989).

Kruse, W., et al., "Nocturnal Inhibition of Lipolysis in Man by Nicotinic Acid and Derivatives," Eur. J. Clin. Pharmacol., 16:11-15 (1979).

Krycer, I., et al., "An Evaluation of Tablet Binding Agents Part I. Solution Binders," Powder Technol., 34:39-51 (1983).

Laguna, O., et al., "Enrobage. III. Influence de quelques produits filmogènes et plastifiants sur la dissolution de comprimès à base de chlorure de sodium," ("Coatings. III. Influence of various filmogenic products and plasticizers on the dissolution of tablets with a sodium chloride base") Ann. Pharm. Fr., 33(5):235-242 (1975). This document relates to the dissolution properties of sodium chloride-based tablets coated with filmogenic products and plasticizers.

Lapidus, H., et al., "Some Factors Affecting The Release of a Water-Soluble Drug from a Compressed Hydrophilic Matrix," J. Pharm. Sci., 55(8):840-843 (1966).

Lapidus, H., "Drug Release from Compressed Hydrophilic Matrices," *University Microfilms International*, Thesis, Rutgers University, 1-117 (1967).

Lapidus, H., Chemistry, Abstract, (order No. 67-14,728) 2363-B2364-B (1967).

Lapidus, H., et al., "Drug Release From Compressed Hydrophilic Matrices," J. Pharm. Sci., 57(8):1292-1301 (1968).

Leiner, P., Chain Drug Review Publication, 12 (Jun. 6, 1988).

Luria, M.H., "Effect of Low-Dose Niacin on High-Density Lipoprotein Cholesterol and Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio," Arch. Intern. Med., 148:2493-2495 (1988).

Mahl, M., et al., "A Long Term Study of the Effect of Nicotinic Acid Medication on Hypercholesteremia," Am. J. Med. Sci., 64:673-677 (1963).

Malkowska, S., et al., "Effect of Re-Compression on the Properties of Tablets Prepared by Moist Granulation," Drug Dev. Indust. Pharmacy, Marcel Dekker, Inc., 9(3):349-361 (1983).

Manninen, M., et al., "Lipid Alterations and Decline in the Incidence of Coronary Heart Disease in the Helsinki Heart Study," JAMA, 260(5):641-651 (1988).

Merck & Co. Inc., The Merck Index, Tenth Ed., 809, 520, 351, 466 (1983).

Miettinen, T.A., "Diurnal Variation of LDL and HDL Cholesterol," Ann. Clin. Res., 12:295-298 (1980).

Miettinen, T.A., "Cholesterol Precursors and Their Diurnal Rhythm in Lipoproteins of Patients with Jejuno-Ileal Bypass and Ileal Dysfunction," Metabolism, 34(5):425-430 (May 1985).

Miettinen, T.A. "Diurnal Variation of Cholesterol Precursors Squalene and Methyl Sterols in Human Plasma Lipoproteins," J. Lipid Res., 23:466-473 (1982).

Miettinen, T.A., "Detection of Changes in Human Cholesterol Metabolism," Ann. Clin. Res., 2:300-320 (1970).

Miller, O.N., et al., "Investigation of the Mechanism of Action of Nicotinic Acid on Serum Lipid Levels in Man," Am. J. Clin. Nutr., 8:480-490 (1960).

Muller, J.E. et al., "Circadian Variation in the Frequency of Sudden Cardiac Death," Circulation, 75(1):131-138 (1987).

Nagy, G. et al., "Untersuchungen über die Textur und die Eigenschaften von Acetylsalicylsäure-Tabletten 1. Mitteilung: Ein Fluß der Herstellung-sweise auf die Eigenschaften der Tabletten," ("The texture and properties of acetylsalicylic acid tablets. 1. The effect of manufacturing methods on the properties of tablets") Pharmazie, 33(1):747-749 (1978). This document relates to the effect of manufacturing methods on the properties and textures of acetylsalicylic acid tablets.

Neuvonen, P.J., et al., "The Bioavailability of Sustained Release Nicotinic Acid Formulations," Br. J. Clin. Pharmacol., 32:473-476 (1991).

Pinter, E.J. et al., "Biphasic Nature of Blood Glucose and Free Fatty Acid Changes Following Intravenous Nicotinic Acid in Man," J. Clin. Endocrinol. Metab., 27:440-443 (1967).

Pintye-Hodi, K., et al., "Untersuchungen űber die Textur und die Eigenschaften von Acetylsalicylsäure-Tabletten 2. Mitteilung: Untersuchung der Textur durch Feuchtgranulierung bereiteter Tabletten," Pharmazie, 35(3):168-170 (1980) (with English translation of Abstract attached).

Rader, J.I., et al., "Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin," Am. J. Med., 92:77-81 (1992).

Remington's Pharmaceutical Sciences, 15<sup>th</sup> Ed., 1242-1251, Mack Publishing Co., Easton, PA (1975).

\*\* Remington's Pharmaceutical Sciences, 18<sup>th</sup> Ed., 1636-1637, Mack Publishing Co., Easton, PA (1990).

†Remington's Pharmaceutical Sciences, 1304-1323; 1676-1686, Mack Publishing Co. Easton, PA (1990).

Renzetti, A.R., et al., "Further Assessment of Glunicate Hypolipidaemic Activity in the Rat," J. Pharm. Pharmacol., 37(12):906-909 (1985).

Ross, R. "The Pathogenesis of Atherosclerosis-An Update," N. Engl. J. Med., 314:488-500 (1986).

Rowland, M., et al., Clinical Pharmacokinetics: Concepts and Applications, Les & Feiger, 111 (1980).

Salomon, J-L., et al., "Importance de la technologie et de la formulation pour le mécanisme de libération du chlorure de potassium contenu dans des matrices hydrophiles 1. Influence de la viscosité et du pourcentage de gélifiant," ("Importance of technology and formulation for the mechanism of continuous liberation of potassium chloride from hydrophilic matrices. 1. Effect of viscosity and percentage of excipient") Pharm. ACTA Helv., 54(3):82-85 (1979) (with English translation of Abstract).

Salomon, J-L., et al., "Sustained Release of a Water-Soluble Drug from Hydrophilic Compressed Dosage Forms," *Pharm. Ind.*, 41(8):799-802 (1979).

Schlierf, G., et al., "Diurnal Patterns of Triglycerides, Free Fatty Acids, Blood Sugar, and Insulin During Carbohydrate-Induction in Man and Their Modification by Nocturnal Suppression of Lipolysis," J. Clin. Invest., 52:732-740 (1973).

Schlierf, G., et al., "Inhibition of Carbohydrate-Induced Hypertriglyceridemia by Nicotinic Acid," Artery, 3(2):174-179 (1977).

Schlierf, G., et al., "Diurnal Patterns of Plasma Triglycerides and Free Fatty Acids in Normal Subjects and in Patients with Endogenous (Type IV) Hyperlipoproteinemia," Nutr. Metabol., 13:80-91 (1971).

Schlierf, G., et al., "Modification of 'Carbohydrate-Induced' Triglyceridemia by Nocturnal Suppression of Lipolysis - Comparison of Nicotinic Acid and Glucose," Pharmacological Control of Lipid Metabolism, Proceedings of the Fourth International Symposium on Drugs Affecting Lipid Metabolism, Philadelphia, PA, 26:319-320 (1971).

Schulman, K.A., et al., "Reducing High Blood Cholesterol Level With Drugs - Cost-effectiveness of Pharmacologic Management," JAMA, 264(23):3025-3033 (1990).

Shepherd, J., et al., "Effects of Nicotinic Acid Therapy on Plasma High Density Lipoprotein Subfraction Distribution and Composition and on Apolipoprotein A Metabolism," J. Clin. Invest., 63:858-867 (1979).

Sokoloski, T.T., "Solutions and Phase Equilibria," Remington's Pharmaceutical Sciences, 17<sup>th</sup> Ed., 207-208, Mack Publishing Co., Easton, PA (1985).

Sprengers, E.D., et al., "Plasminogen Activator Inhibitors" Blood, 69(2):381-387 (1987).

Squires, R.W., et al., "Low-Dose, Time-Release Nicotinic Acid: Effects in Selected Patients With Low Concentrations of High-Density Lipoprotein Cholesterol," Mayo Clin. Proc., 67(9):855-860 (1992).

Subissi, A., et al., "Acute Effects on Plasma Lipids in the Rat of a New Long-Acting Nicotinic Acid Derivative: LG 13979," J. Pharm. Pharmacol., 35:571-575 (1983).

Svedmyr, N., et al., "The Relationship Between the Plasma Concentration of Free Nicotinic Acid and Some of Its Pharmacologic Effects in Man," Clin. Pharm. Ther., 4(10):559-570 (1969).

Urberg, M., et al., "Evidence for Synergism Between Chromium and Nicotinic Acid in the Control of Glucose Tolerance in Elderly Humans," Metabolism, 36(9):896-899 (1987).

Urburg, M., et al., "Hypocholesterolemic Effects of Nicotinic Acid and Chromium Supplementation," J. Family Practice, 27(6):603-606 (1988).

Wahlberg, G., et al., "Effects of Nicotinic Acid on Concentrations of Serum Apolipoproteins B, C-1, C-II, C-III and E in Hyperlipidemic Patients," Acta Med. Scand., 224:319-327 (1988).

Wiman, B., et al., "The Role of the Fibrinolytic System in Deep Vein Thrombosis," J. Lab. Clin. Med., 105(2):265-270 (1985).

The above-identified application is a continuation-inpart of United States application 08/814,974 ("the '974
application), filed March 6, 1997, now United States patent
6,129,930 ("the '930 patent"); which is a continuation-in-part
of United States application 08/368,378, filed January 14, 1995,
now United States patent 6,080,428 ("the '428 patent"); which is
a continuation-in-part of United States application 08/124,392,
filed September 20, 1993, now abandoned.

Applicant makes of record the documents listed below, from litigations involving the '930 patent, the '428 patent and United States patent 6,406,715, which claims priority from the '974 application:

- \*\* Complaint, filed by Kos Pharmaceuticals, Inc. against Barr Laboratories on March 4, 2002, in Civil Action No. 02 CV 1683.
- \*\* First Amended Complaint, filed by Kos Pharmaceuticals, Inc. on March 11, 2002, in Civil Action No. 02 CV 1683.
- \*\* Answer To First Amended Complaint, filed by Barr Laboratories on March 25, 2002, in Civil Action No. 02 CV 1683.
- \*\* Reply To Counterclaims, filed by Kos Pharmaceuticals, Inc. on April 15, 2002, in Civil Action No. 02 CV 1683.
- \*\* Amended Answer To First Amended Complaint, filed by Barr Laboratories on August 19, 2002, in Civil Action No. 02 CV 1683.
- \*\* Complaint, filed by Kos Pharmaceuticals, Inc. on August 13, 2002, in Civil Action No. 02 CV 6409.

- \*\* Answer To Complaint, filed by Barr Laboratories on September 3, 2002 in Civil Action No. 02 CV 6409.
- \*\* Complaint, filed by Kos Pharmaceuticals, Inc. on November 12, 2002, in Civil Action No. 02 CV 8995.
- \*\* Answer To Complaint, filed by Barr Laboratories on December 3, 2002 in Civil Action No. 02 CV 8995.
- \*\* Reply To Counterclaims And Counterclaims For Declaratory Judgment, filed by Kos Pharmaceuticals, Inc. on March 4, 2003 in Civil Action No. 02 CV 8995.

The majority of the art cited herein has been previously considered by the Examiner in the applications, from which this application claims priority. Art that is being cited to the Examiner for the first time is indicated by asterisks on this Statement and by a flag on the document itself.

Applicant requests that the above-cited documents be:

(1) fully considered by the Examiner during the course of the examination of this application; and (2) printed on any patent that may issue from this application.

Applicant also requests that a copy of Form PTO-1449, as considered and initialled by the Examiner, be returned to the undersigned with the next Communication.

Respectfully submitted,

Date: 3/17/03

Karen J. Messick (Reg. No. 46,256)

Attorney for Applicant

c/o Kos Pharmaceuticals, Inc.

1001 Brickell Bay Drive

25th Floor

Miami, Florida 33131

Tel.: (305) 523-3643